REMARKS

Claim 25 is pending in the subject application. Applicants have not added or canceled any claims. Applicants have amended claim 25 to more particularly point out the subject matter which applicants regard as the invention. Support for amended claim 25 can be found in the specification at, *inter alia*, page 17, lines 19-25 and page 23, line 15 to page 24, line 38.

Accordingly, applicants maintain that the amendment to claim 25 does no raise any issue of new matter. Upon entry of this Amendment, amended claim 25 will be pending and under examination.

Withdrawal of Rejection under 35 U.S.C. 103(a)

Applicants acknowledge the Examiner's withdrawal of the rejection of claim 25 under 35 U.S.C. §103(a) as being unpatentable over Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104) in view of Benedict et al. (of record) and in view of the product use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision May 27, 1997), as set forth on page 3 of the October 17, 2008 Office Action.

Withdrawal of Rejection on the Ground of Nonstatutory Obviousness-Type Double Patenting

Applicants acknowledge the Examiner's withdrawal of the rejection of claim 25 on the ground of nonstatutory obviousness-type double patenting over claims 1-19 of U.S. Patent No. 6,316,403 in view of Toledo-Pereyra (of record) in view of Benedict et al. (of record) and in view of the product

use sheet from 1,5-dansyl-Glu-Gly-Arg chloromethyl ketone from Calbiochem (revision May 27, 1997), as set forth on page 4 of the October 17, 2008 Office Action.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claim 25 under 35 U.S.C. 103(a) as allegedly obvious over:

(1) Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104, of record) in view of Benedict et al. (J. Clin Invest., 1991, of record on the 9/20/04 IDS) in view of WO 97/42900 (Rose et al. 1997) and in view of Ludwig et al. (Blood, 1992, 79:1225-1232); and

(2) Toledo-Pereyra (Klin Wochenschr, 1991, 69:1099-1104, of record) in view of Benedict et al. (J. Clin Invest., 1991, of record on the 9/20/04 IDS) in view of U.S. Patent 5,839,443 (issued 1998 to Rose et al.) and in view of Ludwig et al. (Blood, 1992, 79:1225-1232).

Examiner's Rejection

Specifically, the Examiner asserts that Toledo-Pereyra discloses that at the time the instant invention was made, a skilled artisan knew that "reperfusion injury" was often referred to by the descriptive physiological pathological process of thrombosis (see entire document, particularly the right column of page 1099). The Examiner further notes that Toledo-Pereyra also discloses that fibrinogen activation and clotting (i.e. thrombosis) is a pathophysiological event in

reperfusion injury that needs to be treated with pharmacological agents such as heparin to inhibit coagulation (see particularly the right column of page 1099, Table 7, and the right column of page 1103). However, the Examiner acknowledged that the teachings of Toledo-Pereyra does not disclose the administration of "factor IXa compounds" to treat thrombosis in reperfusion injury, which is indicated in the instant claimed invention.

According to the Examiner, Benedict et al. disclose that inactivated factor IXa was successfully used to inhibit thrombus formation in vivo (see entire document, particularly the abstract). The Examiner asserts that Benedict et al. further disclose that administration of inactivated factor IXa offers an advantage over the administration of heparin for inhibiting coagulation in that animals treated with heparin suffered from excessive bleeding while animals given inactivated factor IXa did not manifest excessive bleeding (see particularly Figure 4). The Examiner asserts that Benedict et al. disclose making inhibited factor IXa by incubating factor IXa with glu-gly-arg-chloromethyl ketone (see particularly the right column of page 1760).

According to the Examiner, WO 97/42900 (Rose et al., 1997) and U.S. Patent 5,839,443 (Rose et al., 1998) disclose methods of inhibiting thrombus formation in vivo using inactivated factor IXa compounds, such compounds being disclosed as including factor IXa inactivated with glu-gly-arg-chloromethyl ketone as well as recombinant factor IX polypeptides wherein amino acids at the active site, particularly the active site serine, are mutated (see entire document of WO 97/42900, particularly

pages 8 and 9 and entire document of U.S. Patent 5,839,443, particularly column 4).

According to the Examiner, Ludwig et al. disclose that the active site of factor IX comprises His221, Asp269 and Ser365, and further discloses multiple mutant factor IX polypeptides that are enzymatically inactive due to substitution mutations at these positions (see entire document, particularly the abstract).

The Examiner asserts that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer inactivated factor IXa to patients to treat reperfusion injury. According to the Examiner, the motivation to do so at the time the invention was made comes from the teachings of Toledo-Pereyra that thrombus formation in reperfusion injury is to be treated with heparin and the teachings of Benedict et al. that inactivated factor IXa is better than heparin at inhibiting thrombus formation in vivo because unlike heparin, inactivated factor IXa administration does not lead to excessive bleeding. The Examiner further asserts a person of ordinary skill in the art would have been further motivated to substitute factor IX polypeptides comprising active site substitution mutations, such as those disclosed by Ludwig et al. for the chemically inactivated factor IX of Benedict et al. based upon the disclosure of Rose et al. that both chemically inactivated and recombinantly produced mutant factor IX polypeptides are to be used in methods of inhibiting coagulation. The Examiner notes that this is because both the chemically inactivated and mutant factor IX polypeptides are enzymatically inactive.

Applicants' Response

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that contrary to the Examiner's position, the primary reference, Toledo-Pereyra et al., does not teach that "reperfusion injury" is synonymous with "thrombosis." In particular on page 1099 as cited by the Examiner, Toledo-Pereyra et al. makes it clear that "reperfusion injury" encompasses a number of pathophysiological events, only one of which is thrombosis. Moreover, Toledo-Pereyra et al. distinguishes between these pathophysiological events, for example on page 1099, first paragraph, referring separately to "outflow block," "congestion," "insufficiency," and "thrombosis." Thus there is no suggestion in Toledo-Pereyra et al. that treating thrombosis is somehow equivalent to treating "reperfusion injury." Applicants further note that claim 25 is directed to healing "reperfusion injury." The remaining cited references in combination with Toledo-Pereyra et al. do not cure this deficiency of the combined references' failure to teach a method of treating reperfusion injury.

In addition, without conceding the correctness of this rejection, applicants have herewith amended claim 25. As amended, claim 25 recites factor IXa compounds not disclosed in the combination of the cited references. Applicants note that nowhere do the cited references teach or suggest the specific factor IXa compounds recited in claim 25.

In view of the amendment to claim 25 and the preceding remarks, applicants respectfully request that the Examiner

reconsider and withdraw the rejections of claim 25 under 35 U.S.C. §103(a).

Double Patenting Rejection

The Examiner further rejected claim 25 on the ground of nonstatutory obviousness-type double patenting over claims 1-19 of U.S. Patent No. 6,316,403, in view of:

(A) Toledo-Pereyra (1991) in view of Benedict et al. (1991) in view of WO 97/42900 (Rose et al. 1997) and in view of Ludwig et al. (1992); and

(B) Toledo-Pereyra (1991) in view of Benedict et al. (1991) in view of US Patent 5,839,443 (Rose et al. 1998) and in view of Ludwig et al. (1992).

In response, and without conceding the correctness of the Examiner's rejection, applicants note that claim 25, as amended, does not recite the multiple mutant factor IX polypeptides disclosed in Ludwig et al. (1992). Applicants further note that nowhere does the combination of cited references teach or suggest the specific factor IXa compounds recited in claim 25. Moreover, claims 1-19 of U.S. Patent No. 6,316,403 recite administering inactivated factor IX, and not factor IXa compounds as recited in claim 25 of the current invention.

Accordingly, applicants maintain that claim 25 is not obvious over claims 1-19 of U.S. Patent No. 6,316,403, in view of Toledo-Pereya, Benedict, et al., WO 97/42900 (Rose et al.

1997), U.S. Patent No. 5,839,443 (Rose et al. 1998), and Ludwig et al.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection on the grounds of nonstatutory obviousness-type double patenting.

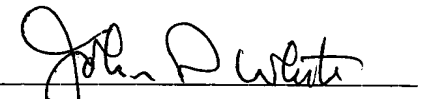
Summary

In view of the amendment to claim 25 and the preceding remarks, applicants maintain that amended claim 25 is in condition for allowance, and respectfully request that the Examiner issue a notice of allowance.

If a telephone interview would be of assistance in resolving any issue in connection with this Petition, applicants' undersigned attorney invites the Patent Office to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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